The biopharmaceutical classification of Excipients – a new era for excipients

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In the last couple of decades the pharmaceutical excipients industry has been highly active pursuing new excipients able to overcome the market needs. Among these needs are the highly specific functional excipients for drug delivery and excipients able to interfere with our biological barriers. Regarding the later, the development of excipients able to interfere with the intestinal metabolism and efflux mechanisms were among the top priorities [1]. This text will focus on the excipients able to interfere with our biological systems in the gastrointestinal tract.

At this stage it is possible to denote that a huge progress was made and a lot of new excipients were developed. Among these, polymeric surfactants were the ones presenting more potential to interfere and affect our intestinal biological mechanisms and thus improving drug performance [2].

Intestinal defense mechanisms, such as intestinal metabolism and efflux mechanisms are playing an important role in decreasing the bioavailability of drugs, particularly relevant in drugs belonging to the BCS classes II, III and IV, which represent the majority of drugs currently under development [3].

Intestinal metabolism mechanisms refer to enzymes present in intestinal mucosa. Cytochrome P450 (CYPs) are of particular importance, being responsible for the majority of phase I drug metabolism reactions. From these, CYP3A and CYP2C are the most representative in the intestinal mucosa, in which, CYP3A4, CYP3A5 and CYP2C9 are the most representative in this order of relevance[4]. Intestinal efflux transporters include, P-glycoprotein (P-gp), multidrug resistance proteins (MRP2), organic anion-transporting polypeptide (OATP) and breast cancer resistance protein (BCRP) as most important [5].

Recently a biopharmaceutical classification system of excipients (BCSE) was proposed as tool for better understanding of excipients biological mechanisms. This classification can be a key element for formulators and regulatory authorities [2].

The BCSE classifies the excipients in four classes depending on its ability to interfere with metabolization and /o or intestinal efflux [2].

The BCSE class I includes excipients that do not affect with intestinal metabolism and efflux mechanisms. BCSE class II include excipients that can interfere in the intestinal metabolism mechanisms and not in the intestinal efflux. BCSE class III, only interfere with intestinal efflux mechanisms and not with metabolization mechanisms. The BCSE class IV, include excipients that affect with both intestinal metabolism and efflux mechanisms [2].

Formulators can use this classification to better select the excipients present on the formulation in order to maximize their drugs potential during development phase. These would allow a rationale selection of excipients based not only on the drug and dosage form properties but also including the biological impact of excipients. For instance, drugs that present highly intestinal metabolization, may be formulated with excipients from BCSE classes II or IV, which are able to interfere and reduce its metabolization and therefore maximizing its bioavailability. Generally, it is possible to state that excipients from BCSE class I will present low biological beneficial effect.

Excipients form BCSE classes II and III will present biological beneficial effected depending on the drug properties. The excipients belonging to BCSE class IV are the ones with more potential to provide biological beneficial effects on the formulation [2].

At same time, the BCSE can be an important instrument for regulatory agencies. It would allow agencies to better manage the safety, quality and efficacy risks associated to the use of excipients. This is particularly relevant considering the increase amount of generic products. Formulations containing excipients form BCSE class I present low risk. Formulations with excipients form BCSE class II and III moderate risk depending on the API properties. The higher risk would be associated to excipients BCSE class IV [2].

Unfortunately and despite the advance in the excipients field there is still a huge gap between *in vitro* evidence of biological interference of excipients and it *in vivo* impact. This is mainly due to the lack of specific *in vitro* models for different biological mechanisms but also due to an absence of specific inhibitors since most of them, interfere with different biological mechanisms at same time. Another current limitation is the translation of *in vitro* data to *in vivo* data due to formulation translation constrains, such as unfeasible dosage weight or unacceptable amount of surfactants due to toxicity [2,6].

Despite these limitations, the potential of excipients to interact with our biological barriers is unquestionable and should be subject of a deeply scrutiny [2].

1. References

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